BENZIDINE AND
DYES METABOLIZED TO BENZIDINE

INTRODUCTION

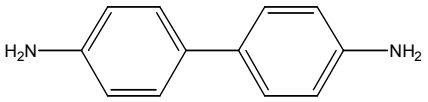
Benzidine was listed in the First Annual Report on Carcinogens (RoC) in 1980. Dyes metabolized to Benzidine (Benzidine Dyes Class) were listed in the Ninth Edition of the RoC in 2000. Two representative dyes of this class, Direct Black 38 and Direct Blue 6, were originally listed in the Third Annual RoC in 1983 as reasonably anticipated to be human carcinogens, and then changed to *known to be human carcinogens* in the Ninth Edition in 2000.

The profile for dyes metabolized to benzidine supercedes the previous listing of individual benzidine dyes (specifically Direct Black 38 and Direct Blue 6) and applies to all dyes that are metabolized to benzidine. The listings for benzidine and dyes metabolized to benzidine in the Tenth Edition of the RoC are as follows:

Benzidine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1982, 1987).

Benzidine dyes that are metabolized to benzidine are *known to be human carcinogens* based on the fact that benzidine is a known human carcinogen and that metabolism of benzidine-based dyes to release free benzidine is a generalized phenomenon in all species studied, including humans; benzidine exposure following exposure to benzidine-based dyes is equivalent to exposure to equimolar doses of benzidine (Lynn *et al*. 1980); and all available evidence indicates benzidine-based dyes are animal carcinogens and represent a carcinogenic risk to humans (NCI 1978, IARC 1982, 1987).

BENZIDINE
CAS No. 92-87-5
First listed in the *First Annual Report on Carcinogens*



CARCINOGENICITY

Benzidine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1982, 1987). Case reports and follow-up studies of workers provide sufficient evidence that occupational exposure to benzidine is strongly associated with an increased risk of bladder cancer. The association is strengthened by data that suggest that the incidence of this cancer in workers decreased after a reduction in industrial exposure.

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of benzidine in experimental animals (IARC 1982, 1987). When administered in the diet, benzidine induced urinary bladder carcinomas in dogs and increased the incidence of benign and malignant cholangiomatous tumors and hepatocellular tumors in hamsters of both sexes. When administered by gavage, benzidine induced multiple mammary carcinomas in female rats. When administered by subcutaneous injection, benzidine induced hepatocellular carcinomas and adenomas and cholangiomas in mice of both sexes. When administered by subcutaneous injection, benzidine induced hepatomas, cystocholangiomas, or hepatocellular carcinomas, tumors of the Zymbal gland, and local sarcomas in rats of both sexes. In another study, subcutaneous injection induced mammary adenocarcinomas in female rats. When administered by intraperitoneal injection, benzidine induced a dose-related increase in the incidence of benign and malignant mammary tumors and adenomas and carcinomas of the Zymbal gland in female rats.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Covalent binding products of benzidine with DNA have been described in the liver of mice and rats treated *in vivo*. Micronuclei, sister chromatid exchanges, DNA strand breaks and unscheduled DNA synthesis were induced in cells of rodents treated in vivo. Benzidine caused transformation of Syrian hamster embryo and BALB/c 3T3 cells and induced chromosomal aberrations, sister chromatid exchanges, unscheduled DNA synthesis and DNA strand breaks in rodent cells *in vitro*; conflicting results were obtained for mutations. Aneuploidy, gene conversion and DNA damage were induced in yeast, but not mutations. It was mutagenic to plants and bacteria (IARC 1987).

PROPERTIES

Benzidine occurs as a grayish yellow, white, or reddish-gray crystalline powder but darkens on exposure to air and light. It is slightly soluble in water, boiling alcohol, and ether. As a weak base, benzidine can form insoluble salts with sulfuric acid. Benzidine does not readily ignite but will ignite spontaneously with red fuming nitric acid. The technical grade is 80 to 85% paste or powder. When heated to decomposition, it emits highly toxic fumes of nitrogen oxides (HSDB 2001).

USE

Benzidine has been used for more than 60 years as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds. More than 250 benzidine-based dyes have been reported (IARC 1982). Benzidine-based dyes are used primarily for dyeing textiles, paper, and leather products. There are approximately 550 dye applications. Approximately 50% of the dyes were applied to textiles, 45% to paper, and 5% to leather (NCI 1975). Benzidine is also used as a reagent for hydrogen peroxide in milk, a staining agent in microscopy, a stiffening agent in rubber compounds, a laboratory reagent for the detection of hydrogen cyanide and sulfate, for quantitative determination of nicotine, and as a spray reagent for sugars (HSDB 2001). In recent years, general use of benzidine has fallen dramatically because of its potential carcinogenicity (IARC 1982).

PRODUCTION

Benzidine is no longer manufactured for commercial sale in the United States (IARC 1982, ATSDR 2001). All large-scale production was discontinued in 1976 and relatively small quantities remain for diagnostic testing (HSDB 2001). The Chem Sources International directory identified 11 current U.S. suppliers (Chem. Sources 2001). Currently, all benzidine production is for captive consumption and it must be maintained in closed systems under stringent workplace controls (ATSDR 2001). An estimated production of only 227 kg (500 lb) was reported for 1983, though this may omit some captive production (ATSDR 2001). The 1979 TSCA Inventory identified one company producing 500 lb of benzidine in 1977 (TSCA 1979). Prior to 1977, U.S. production of benzidine amounted to millions of lb per year (IARC 1982).

In recent years, there have been no imports of benzidine, but benzidine-based dyes, such as Direct Black 38, are still imported. The latest figure found was for 1980, when 8900 lb of benzidine was imported into the United States (ATSDR 2001). Data on exports could not be located.

EXPOSURE

The primary routes of potential human exposure to benzidine are inhalation, ingestion, and dermal contact. Benzidine may get into the respiratory tract from accidental releases into the air; into the gastrointestinal tract from contaminated fingers, cigarettes, or food; and onto the skin directly or from contaminated clothing and gloves (NCI 1975). Before 1974, benzidine and its derivatives were manufactured and used in open systems that permitted atmospheric releases at the workplace. Under OSHA regulations adopted in 1974, only closed systems were permitted. Although atmospheric emissions were expected to be reduced because of these regulations, no data were available that reflected current concentrations of benzidine in air (ATSDR 2001).

The major release routes of benzidine to the environment appear to be by wastewaters and sludges, and by solid wastes generated by the use of benzidine and production of benzidine-based dyes. The median concentrations of benzidine in waste effluents, ground water, surface water, and soils appear to be low, probably because significant levels are associated with localized areas of contamination. The production and utilization of benzidine-based dyes has decreased in the last 30 years, and environmental and health regulations have been implemented to reduce release of benzidine to the environment (ATSDR 2001).

Although the risk of the general population from benzidine is not known, available data suggest the potential for exposure via environmental media is low. For food, low levels can be found in synthetic coloring agents added to some prepared foods, which, once ingested, can be metabolized into benzidine; this, however, poses a low risk (ATSDR 2001).

In most cases, benzidine is a hazard only in the vicinity of dye and pigment plants where wastes may escape or be discharged. Since benzidine is no longer commercially produced or used in the U.S., the potential for occupational exposure to this compound is low (ATSDR 2001). The National Occupational Exposure Survey (1981-1983) indicated that 15,554 workers, including 426 women, potentially were exposed to benzidine (NIOSH 1984). The NIOSH numbers were not based on actual measurements. Workers in the United States routinely wear protective equipment to eliminate inhalation and skin contact (ATSDR 2001).

Benzidine total on-site and off-site releases for the years 1993, 1994, and 1999 were 16, 250, and 7 lbs (for original industries), respectively. In 1999 six facilities (all industries) reported releasing 178 lbs of benzidine of which 93% was released off-site (TRI99 2001).

REGULATIONS

EPA regulates benzidine under the Clean Water Act (CWA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), the Superfund Amendments and Reauthorization Act (SARA), and the Toxic Substances Control Act (TSCA). Effluent discharge guidelines have been set under CWA, and benzidine is subject to reporting rules under CWA, SARA, and TSCA. The CERCLA reportable quantity (RQ) for benzidine is 1 lb (0.454 kg). It is regulated as a hazardous constituent of waste under RCRA.

FDA, under the Food, Drug, and Cosmetic Act (FD&CA), also regulates the amount of benzidine in various color additives for use in food, drugs, and cosmetics. The benzidine concentration in food colorants is limited to 1 ppb, except for D&C Red No. 33, which can contain up to 20 ppb benzidine.

NIOSH recommends reducing benzidine exposure levels to the lowest feasible concentration. OSHA, which has set a established protective standards for occupational exposure to benzidine, regulates benzidine under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 20.

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TSCA. Toxic Substances Control Act, Chemical Substance Inventory, 1979: public record.

DYES METABOLIZED TO BENZIDINE (BENZIDINE DYE CLASS)*

First listed in the *Ninth Report on Carcinogens*

CARCINOGENICITY

Benzidine-based dyes that are metabolized to benzidine are *known to be human carcinogens* based on the fact that (1) benzidine is a known human carcinogen (IARC 1972, 1979, 1982a, 1987), (2) metabolism of benzidine-based dyes to release free benzidine is a generalized phenomenon in humans and all experimental animal species studied, (Rinde and Troll 1975, Lynn et al. 1980, Nony et al. 1980, Lowry *et al*. 1980, Martin and Kennelly 1985), and (3) benzidine exposure from exposure to benzidine-based dyes is equivalent to exposure to equimolar doses of benzidine (Lynn *et al*. 1980).

The evidence that benzidine-based dyes that are metabolized to benzidine are human carcinogens is supported by experimental animal studies which have shown that all benzidine-based dyes that have been tested in experimental animals are animal carcinogens and therefore represent a carcinogenic risk to humans (NCI 1978, IARC 1982a,b).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Benzidine was one of the first chemicals for which an association of occupational exposure and increased cancer was recognized for humans. Increased incidences of urinary bladder cancer in humans were concluded to result from industrial exposure by the International Labor Office in 1921 (IARC 1982a). Since that time, several IARC and NTP committees (IARC 1972, 1979 1982a, 1987) have concluded that benzidine and its salts are carcinogens in numerous species including rats, mice, hamsters, dogs, and humans. The primary target organs for carcinogenicity induced by benzidine vary with species. Rats, mice, and hamsters develop increased incidences of hepatocellular carcinomas, mammary carcinomas in female rats, and Zymbal gland tumors in both sexes of rats. Dogs and humans develop increased incidences of urinary bladder cancer.

The first dyes based on the benzidine molecule were synthesized more than 100 years ago. Since a wide spectrum of colors could be achieved by varying the molecules' chromophores, linked to benzidine by an azo linkage (-N=N-), this facile and productive synthesis resulted in many excellent dyes. The variety of dyes based on benzidine is exemplified by the fact that 258 benzidine-based dyes were listed in the third edition of the Colour Index (Martin and Kennelly 1985). Each of these dyes was formed by diazotization of benzidine with nitrous acid and then coupling the resulting diazonium salt with various chromophores to form compounds with azo linkages. Similar or different chromophores may be linked at each amino group of the benzidine molecule to form various bis-azobiphenyl dyes. However, regardless of the chromophore(s) involved, the azo linkages of all benzidine-based dyes are essentially chemically equivalent.

Just as the azo linkages between benzidine and chromophores are easily formed chemically, they are also easily broken by chemical or enzymatic reduction. Products of reductive cleavage of the dyes are free benzidine and the respective chromophores. One of the first reports of reductive cleavage of a benzidine-based dye in a biological system

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* No CAS registry number is assigned to dyes metabolized to benzidine.

was that of Rinde and Troll (1975). That report indicated that each of four benzidine-based dyes was reduced to benzidine by primates, most probably by gastrointestinal bacteria. Later reports provided evidence that benzidine-based dyes are metabolized to free benzidine by humans (Lowry *et al*. 1980) and also rats and dogs (Lynn *et al*. 1980), and hamsters (Nony *et al*. 1980). Lowry *et al*. (1980) concluded that the amount of benzidine and its metabolites detected in urine of exposed workers could not have been accounted for by the minute amounts of free benzidine in the dyes to which they were exposed. Thus, evidence was provided to indicate that humans also metabolize benzidine-based dyes to free benzidine. The conclusion to be drawn from this series of studies is that reduction of benzidine dyes to release benzidine was a generalized phenomenon that occurred in most, if not all, species. By determining the quantities of benzidine and its metabolites excreted following administration of free benzidine versus three benzidine-based dyes, Lynn *et al*. (1980) also provided quantitative data for the reduction of benzidine-based dyes to free benzidine. Results of that study indicated evidence that each of the dyes studied was reduced to an amount of free benzidine equal to that observed from an equimolar dose of benzidine. Thus, the first evidence was provided to indicate that ingestion of benzidine-based dyes was equivalent to exposure to an equimolar dose of free benzidine.

Since occupational exposure to benzidine-based dyes has been most frequently associated with co-exposure to benzidine, it has been difficult to clearly establish their carcinogenicity in humans. Two recent studies have endeavored to address this problem by studying Chinese workers who remained in the same jobs for many years. Results of these studies were mixed. Whereas, You *et al*. (1990) observed no increased incidence of tumors in workers exposed almost exclusively to benzidine-based dyes, Bi *et al*. (1992) reported that cancer incidences were elevated for workers exposed to both benzidine and benzidine-based dyes. Unfortunately, neither report was able to adequately document levels of exposure to either benzidine or the dyes. Evidence for the carcinogenicity of benzidine-based dyes in laboratory animals has been provided by studies in which three dyes, Direct Blue 6, Direct Black 38, and Direct Brown 95, were positive liver carcinogens in rats following an exposure of only 13 weeks (NCI 1978, IARC 1982a,b). The IARC evaluation of these results and benzidine-based dyes in general reached the following conclusion. "Although the epidemiological data were inadequate to evaluate the carcinogenicity to man of individual benzidine dyes, they, together with the presence of benzidine in the urine of exposed workers, provide *sufficient evidence* that occupational exposure to benzidine-based dyes represents a carcinogenic risk to man."

PROPERTIES

Benzidine can be found as white or slightly reddish crystals or powder. Its density is 1.250 at 20°C/4°C. It is slightly soluble in hot water, boiling ethanol and diethyl ether. The various dyes that metabolize to benzidine have varying colors; from blue, to red, orange, brown and black.

USE

Dyes that metabolize to benzidine are mainly used to color textiles, rubber, plastic products, printing inks, paints, lacquers, leathers, and paper product. Approximately 50% of the dyes are applied to textiles, 45% to paper, and 5% to leather (NCI 1975). While benzidine use has fallen dramatically in recent years due to its potential carcinogenicity, dyes that metabolize to benzidine are still used.

PRODUCTION

Over 22 dyes that metabolize to benzidine have been produced in the U.S. They are marketed under several hundred trade names (NIOSH 1983). In 1978, 1 to 2 million lb of dyes that metabolize to benzidine were produced or imported (NIOSH 1980). U.S. sales and imports of dyes that metabolize to benzidine fluctuated between 1975 to 1978. In 1975, U.S. sales were 4.2 million lb, while imports were 0.9 million lb. Sales peaked in 1976 (6.6 million lb) but steadily declined in 1977 (4.6 million lb) and 1978 (1.9 million lb). Imports slowly rose, with 0.6 million lb being imported in 1976, 1.3 million lb in 1977, and 1.6 million lb in 1978 (EPA 1980).

EXPOSURE

The primary routes of potential human exposure to dyes that metabolize to benzidine are inhalation, ingestion, and dermal contact. These dyes may enter the respiratory tract from accidental releases into the air; into the gastrointestinal tract from contaminated fingers, cigarettes, or food; and onto the skin directly or from contaminated clothing and gloves. While most of the dyes that metabolize to benzidine are only permitted to be used in closed systems, accidental releases of these dyes could lead to occupational and environmental exposure.

In most cases, dyes that metabolize to benzidine are hazards only in the vicinity of dye and pigment plants where wastes may escape or be discharged. The National Occupational Exposure Survey (1981-1983) estimated that 28,442 workers were potentially exposed to dyes that metabolize to benzidine (NIOSH 1984). The National Occupational Hazard Survey (1972-1974) estimated that 20,470 workers were potentially exposed to dyes that metabolize to benzidine (NIOSH 1976).

REGULATIONS

In 1980, the CPSC collected economic and toxicological data to propose a ban on the use of benzidine-based dyes in direct consumer dye products. CSPC also completes studies on the dermal penetration of two benzidine congener dyes with negative results. The use of benzidine congener dyes in consumer products and commercial textile applications has been decreased voluntarily. Therefore, CSPC did not issue a ban of these consumer dye products. Consumer products containing benzidine congener dyes that are packaged or marketed as art and craft materials may be subject to specific procedural and labeling requirements under the Labeling of Hazardous Art Materials Act (LHAMA).

EPA regulates benzidine under the Clean Water Act (CWA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), the Superfund Amendments and

Reauthorization Act (SARA), and the Toxic Substances Control Act (TSCA). Effluent discharge guidelines have been set under CWA, and benzidine is subject to reporting rules under CWA, SARA, and TSCA. A reportable quantity (RQ) of 1 lb (0.454 kg) has been set for benzidine under CERCLA and it is regulated as a hazardous constituent of waste under RCRA.

FDA, under the Food, Drug, and Cosmetic Act (FD&CA), also regulates the amount of benzidine in various color additives for use in food, drugs, and cosmetics. The benzidine concentration in food colorants is limited to 1 ppb, except for D&C Red # 33, which can contain up to 20 ppb benzidine.

NIOSH has recommended that exposure to benzidine be the lowest feasible concentration. OSHA, which has established protective standards for occupational exposure to benzidine, regulates benzidine under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 20.

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